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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/731,830	12/08/2000	Junji Hamuro	200488US0CONT	6052

22850 7590 08/04/2003

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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 08/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/731,830	HAMURO ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *09/334,647; 09/181,881* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *17* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The finality of previous Office Action mailed February 21, 2003 (Paper No. 16) has been withdrawn because a new ground rejection is applied.

Foreign Priority

2. Applicants claims foreign priority, but has not provide an English translation of the foreign application (Japan 312727, filed 10/29/97, submitted in application 09/181,881). Therefore, the priority date (October 29, 1997) is not perfected.

Status of the Claims

3. Claims 30-47 are pending.

Applicants' Appeal Brief filed on May 21, 2003 (Paper No. 19) is acknowledged, and the comments in the Brief have been fully considered. Claim 30-47 are examined.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 30-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inducing a Th2 response in a subject, or a method of suppressing cellular immune responses in a subject by skewing the TH1/Th2 balance to Th2, comprising reducing the content of reductive glutathione (GSH) in macrophages by administering the cystine compound of formula (I) (structure shown at page 10); or, a method of inducing a Th2 response, or a method of suppressing cellular immune responses in a subject by skewing the TH1/Th2 balance to Th2, comprising reducing the content of GSH in macrophages

by treating with diethyl maleate, ethanol or cyclophosphamide as indicated in the prior art, does not reasonably provide enablement for a method of inducing a Th2 response, or a method of suppressing cellular immune responses in a subject by skewing the TH1/Th2 balance to Th2, comprising reducing the content of GSH in macrophages, wherein administering the compound to reduce the content of GSH is not indicated, or administering a cystine derivative, where the derivative is not defined. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 30-47 encompass a method of inducing a Th2 response in a subject (claims 30, 32, 34-41 and 46), or a method of suppressing cellular immune responses in a subject by skewing the TH1/Th2 balance to Th2 (claims 31, 33, 42-45 and 47), comprising reducing the content of reductive glutathione in macrophages. The specification, however, only discloses cursory conclusions without data supporting the findings, which state that the present invention provides a method of suppression immune responses by administering to a patient in need thereof an effective amount of a composition comprising a substance capable of reducing the content of GSH in macrophages (page 4, lines 7-22). There are no indicia that the present application enables the full scope in view of a method of inducing a Th2 response or of suppressing cellular immune responses in a subject as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breath of the claims, the absence of working

examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breath of the claims:

The breath of the claims is broad and encompasses unspecified variants regarding the step of reducing the content of GSH in macrophages, or the cystine derivatives administered, which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

There are no working examples indicating the claimed methods in association with the variants except for administering the cystine compound of formula (I) (Examples 9, 13, 14, 18, 19 and 25).

(3). The state of the prior art and relative skill of those in the art:

The prior art (Peterson *et al.*, Proc. Natl. Acad. Sci. USA 95, 3071-3076, March 1998) teaches using two immunological models and three methods (treatment with diethyl maleate, ethanol or cyclophosphamide) to deplete GSH *in vitro* or *in vivo*, and the GSH depletion in antigen-presenting cells (APC) such as macrophages leads to a shift away from the typical Th1 cytokine profile and toward Th2 response. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide teachings on various means to reduce the content of GSH in macrophages to be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims encompass a method of inducing a Th2 response in a subject, or a method of suppressing cellular immune responses in a subject by skewing the TH1/Th2 balance to Th2, comprising reducing the content of GSH in macrophages, however, the treating conditions for various compounds to reduce the content of GSH and the in vivo effects of these compounds are not adequately described in the specification, the invention is highly unpredictable regarding the outcome of the treatment.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method of inducing a Th2 response in a subject, or a method of suppressing cellular immune responses in a subject by skewing the TH1/Th2 balance to Th2, comprising reducing the content of GSH in macrophages. The specification indicates the cystine compounds of formula (I) have the activity of reducing the content of GSH in macrophages, and the effects of these cystine compounds in various disease models have also been shown (pages 9-10, 18; Examples 9, 13, 14, 18, 19 and 25). However, the specification has not demonstrated using other means to reduce the content of GSH in macrophages than administering cystine compounds of formula (I), nor has indicated the in vivo effects of other compounds than cystine compounds of formula (I). Moreover, there are no working examples indicating the treating conditions such as dose with other compounds than cystine compound of formula (I). Since the specification fails to provide sufficient teachings on the treating conditions for various compounds other than cystine compounds to reduce the content of GSH in macrophages and the in vivo effects of these compounds, it is necessary to have additional guidance and to carry out further experimentation to assess the effects of various compounds in the claimed method.

(6). Nature of the Invention

The scope of the claims encompasses a method of inducing a Th2 response, or a method of suppressing cellular immune responses in a subject by skewing the TH1/Th2 balance to Th2, comprising reducing the content of GSH in macrophages, but the specification does not demonstrate using various means or compounds in the claimed method. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broader than the enabling disclosure. The working examples do not demonstrate the claimed methods, the outcome of the treatment is unpredictable, and the teaching in the specification is limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effects of using various means or various compounds in the treatment.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 30-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claims 30-45 are indefinite because the claims lack essential steps in the method of inducing Th2 response in a subject, or a method of suppressing cellular immune response in a subject. The omitted step is administering an effective amount of a composition comprising a cystine compound of formula (I), it is unclear how the content of reductive glutathione in macrophage is reduced in the subject in the claimed method. Claims 31 and 32 are also

indefinite because of the use of the term "Th1" or "Th2", it is not clear what term means. Claims 32-45 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

7. Claims 46 and 47 are indefinite because of the use of the term "cystine derivative". The term "cystine derivative" renders the claim indefinite it is not clear what structure the derivative has, and how different the cystine derivative is from the parent compound.

Response to Appeal Brief

In the Appeal Brief, Section (VI) states summary of the invention, the invention is directed to a method of inducing a Th2 response comprising reducing the content of reductive glutathione in macrophages in the subject, thereby increasing the capacity of the macrophages to produce IL-6 and decreasing the capacity of the macrophages to produce IL-12 and NO; or a method of suppressing cellular immune responses in a subject by skewing the TH1/Th2 balance to Th2, comprising reducing the content of reductive glutathione in macrophages in the subject; Section (VII) states the sole issue is whether claims 30-47 are unpatentable under 35 U.S.C. 112, second paragraph; Sections (VIII) states the groups of claims, the claims do not stand or fall together; Section (IX) states appellants' arguments on the claims; Section (X) states the relief requested.

In Appeal Brief, applicants argue that a claim is definite if one skilled in the art can appreciate the metes and bounds of the claims in light of the specification, a claim is not indefinite for failing to recite a claim limitation which is allegedly necessary to define a workable invention, and a claim is not to explain the technology, but to state the legal boundaries of the patent grant; and the claims are directed to a method of inducing a Th2 response or of

suppressing cellular immune in a subject by skewing the Th1/Th2 balance to Th2, and the specification describes 26 working examples related to the practice of the claimed invention (pages 5-60 of the specification; pages 4-11 of the Brief). Applicants' response has been fully considered, however, the arguments on the rejection of claims 30-47 under 35 U.S.C. 112, second paragraph is not found persuasive because the claim does not recite the step of administering cystine compound which is essential for reducing the content of reductive glutathione in the claimed method even the specification provides the teachings, it is not clear how to practice the claimed method, what the metes and bounds of the claims are on reducing the content of reductive glutathione in microphages in the subject, and how the endpoint of the claimed method is reached without citation of this essential step.

Claim Rejections - 35 USC § 102&103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 30 and 31 are rejected under 35 U.S.C. 102(a) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Peterson *et al.* (Proc. Natl. Acad. Sci. USA 95, 3071-3076, March 1998).

Peterson *et al.* teach using two immunological models and three methods (treatment with diethyl maleate, ethanol or cyclophosphamide) to deplete GSH *in vitro* or *in vivo*, and the GSH depletion in antigen-presenting cells (APC) such as macrophages leads to a shift away from the typical Th1 cytokine profile and toward Th2 response, e.g., ethanol-feeding decreases IFN-γ responses and enhances IL-4 in immunized mice, and GSH depletion decreases IFN-γ responses in immunized mice (pages 3071-3072; page 3075, left column; Table 1; claims 31 and 32). The reference also indicates GSH depletion decreases IL-12 production (page 3075, right column, paragraph 5). In the alternative, given GSH depletion in macrophages induces Th2 response, it would have been obvious that the capability of the macrophages to produce IL-6 would be increased and the capability of the macrophages to produce NO would be decreased because these responses are expected in Th2.

Conclusion

9. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, Ph. D. can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

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August 2, 2003

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